Complete Summary

GUIDELINE TITLE

Fludarabine in intermediate- and high-risk chronic lymphocytic leukemia.

BIBLIOGRAPHIC SOURCE(S)

Cancer Care Ontario Practice Guideline Initiative (CCOPGI). Fludarabine in intermediate-and high-risk chronic lymphocytic leukemia [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Feb. Various p. (Practice guideline; no. 6-1). [45 references]

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Intermediate- and high-risk chronic lymphocytic leukemia

GUIDELINE CATEGORY

Assessment of Therapeutic Effectiveness
Treatment

CLINICAL SPECIALTY

Hematology
Internal Medicine
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To make recommendations about the use of fludarabine in patients with intermediate- and high-risk chronic lymphocytic leukemia (CLL)

TARGET POPULATION

- Patients with intermediate-risk chronic lymphocytic leukemia defined as Rai Stage II (lymphocytosis in blood and marrow with enlarged spleen and/or liver [with or without enlargement of nodes]), or Rai Stage III (lymphocytosis in blood and marrow with anemia [hemoglobin <110 g/L])
- Patients with high-risk chronic lymphocytic leukemia defined as Rai Stage IV (lymphocytosis in blood and marrow with thrombocytopenia [platelets <100 X 10^9/L])

INTERVENTIONS AND PRACTICES CONSIDERED

1. Fludarabine (Fludara®) as single agent treatment of intermediate- and high-risk chronic lymphocytic leukemia (CLL)
2. Conventional chemotherapy, such as chlorambucil; cyclophosphamide, vincristine, prednisone (CVP); or cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP)

MAJOR OUTCOMES CONSIDERED

- Primary outcomes: overall survival and quality of life
- Secondary outcomes: progression-free survival and response

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases
Searches of Unpublished Data

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

September 1998 Guideline

A literature search on fludarabine for chronic lymphocytic leukemia was initially undertaken to identify: a) published guidelines, b) meta-analyses or systematic literature reviews, c) randomized controlled trials, and d) controlled clinical trials. MEDLINE (1986-January 1997), CANCERLIT (1994-1997) and PREMEDLINE databases, updated to December 1998, were searched using the following search terms: chronic lymphocytic leukemia (explode and text word) and fludarabine (text word); guidelines (explode) or practice guidelines (explode) or [guideline* or practice guideline* (publication type, subject heading and text word)]; meta-analy: (publication type, subject heading and text word) or metaanaly: (text

word) or [systematic overview * or systematic review* (text word)]; random: (publication type, subject heading and text word); clinical trials (explode and publication type) or multicenter study (publication type) or controlled clinical trial (publication type) or comparative study (subject heading). CARL Corporation's UnCover database was searched for articles which had not yet been indexed in MEDLINE using the keywords chronic lymphocytic leukemia and fludarabine. The Physician Data Query (PDQ) database was searched to find ongoing trials, both those that are actively accruing patients and those that have recently closed. Abstracts from the 1998 American Society of Hematology (ASH) conference proceedings were also reviewed.

February 2002 Update

The original literature search has been updated using MEDLINE (through January 2002), CANCERLIT (through October 2001), Health Star (through December 2000) the Cochrane Library (2002, Issue 1) and the proceedings of the annual meeting of the American Society of Clinical Oncology (2001) and the American Society of Hematology (2001).

Inclusion Criteria

Original: September 1998

Articles were selected for inclusion in the systematic review of the evidence if they met the following criteria:

1. Syntheses of evidence (evidence-based practice guidelines or systematic reviews)
2. Randomized control trials with appropriate comparison groups
3. In the absence of randomized controlled trials, comparative and non-comparative (phase II) studies

Fully published articles and abstracts in English between the years of 1986 and 1998 were selected.

Update: February 2002

At the August 2001 update, the inclusion criteria regarding individual trials were revised to include only randomized controlled trials reporting the primary outcomes of interest. Non-randomized comparative and non-comparative studies are included for toxicity evaluation only.

NUMBER OF SOURCE DOCUMENTS

September 1998 Guideline

Three randomized controlled trials (RCTs) and six phase II studies were reviewed.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Meta-Analysis of Randomized Controlled Trials
Meta-Analysis of Summarized Patient Data
Review
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

This guideline report was developed by the Cancer Care Ontario Practice Guidelines Initiative (CCOPGI), using the methodology of the Practice Guidelines Development Cycle (see companion document by Browman et al). Evidence was selected and reviewed by one member of the Cancer Care Ontario Practice Guidelines Initiative´s Hematology Cancer Disease Site Group (DSG) and methodologists.

September 1998 Guideline

Pooling of data: As overall survival has not been reported definitively in any of the randomized controlled trials, no pooled estimate for survival was calculated for this guideline report. No quality of life data were available for review. Response rates were pooled across trials to obtain a more precise estimate of the effect of fludarabine or the conventional therapies. Response rates of the conventional therapies could be pooled as the patient populations were similar. Pooled response rates provide an estimate of the activity of fludarabine or the conventional therapies, and should not be interpreted as a surrogate measure for overall survival or quality of life. The data were analyzed separately for previously untreated and previously treated patients. There was a lack of uniform criteria used to define response, although many studies employed the National Cancer Institute Working Group criteria. The data were pooled by summing the number of complete and partial responses across trials and dividing this number by the total number of evaluable patients included in all trials. The result was converted to a percentage and the 95% confidence intervals were calculated. The effect of study design on the result was investigated by calculating the pooled response rate for each study design (randomized controlled trial and phase II) separately and in combination.

The data from randomized controlled trials comparing fludarabine with conventional treatment were combined using the Meta-Analyst[0.998] software provided by Dr. J. Lau, Tufts New England Medical Centre, Boston, MA. Data were analyzed using both fixed effects (Mantel-Haenszel) and random effects (DerSimonian and Laird) models. Odds ratios for response rates comparing fludarabine with conventional therapy are presented with 95% confidence intervals (CI), and two sided p-values.

February 2002 Update

The information above remains current.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

September 1998 Guideline

The Provincial Hematology Disease Site Group (DSG) discussed the use of surrogate outcomes, such as response and progression-free survival as endpoints, for the primary outcomes of overall survival and quality of life. Although these outcomes may not be sufficient for a definitive recommendation for fludarabine as the agent of choice, the group felt that improved progression-free survival and response were important measures in their own right. In particular, improved progression-free survival may be a desirable goal for some patients and might translate into improved quality of life. Thus, in previously untreated patients, fludarabine should be considered as a treatment option, along with the conventional therapies (chlorambucil or cyclophosphamide, hydroxydaunomycin, oncovin, prednisone (CHOP). The choice of therapy should be based on patient preference and clinical judgement about the relation between improvements in progression-free survival and relevant clinical outcomes. Patients should be made aware of the increased risk of infection with fludarabine as this may influence choice in therapy.

For previously treated patients, members of the Hematology DSG felt the superior response rates and the trend towards improved progression-free survival made fludarabine an acceptable treatment option. It also may be a favourable choice because of the limited treatment options for previously treated patients.

The Hematology DSG felt that modulating factors such as cost, convenience of administration, patient age, and disease risk should also be considered in choosing among alternative therapies for the treatment of chronic lymphocytic leukemia (CLL).

February 2002 Update

The Hematology DSG concluded that these new data have a minor effect in changing, but do help clarify, treatment recommendations for previously untreated patients with chronic lymphocytic leukemia. Both chlorambucil and fludarabine are recognized to be acceptable treatment options. The choice of therapy will depend upon patient preferences that should take into account the treatment schedule and route of drug administration, the potential for differences in progression-free survival, and the risk of an opportunistic infection. New data allow for these potential differences to be more precisely estimated, and show that fludarabine treatment is associated with longer progression-free survival, a

trend to more infections, including a greater incidence of herpes viruses, and no detectable difference in overall survival.

The Hematology DSG concluded that treatment combining fludarabine with chlorambucil, or another alkylator agent, should be restricted to clinical trials testing given the excessive toxicity and lack of demonstrable benefit observed with this combination when evaluated in a randomized trial.

For previously treated patients, there is no additional evidence provided by the update; original recommendations are unchanged.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

September 1998 Guideline

Practitioner feedback was obtained through a mailed survey of 92 practitioners. The survey consisted of items evaluating the methods, results and interpretive summary used to inform the draft recommendations and whether the draft recommendation should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent at two weeks (postcard) and four weeks (complete package mailed again). The Hematology Cancer Disease Site Group reviewed the results of the survey and made changes to the document, where appropriate.

The practice guideline reflects the integration of the draft recommendations in the External Review process and has been approved by the Hematology Disease Site Group and the Practice Guideline Coordinating Committee.

February 2002 Update

The original practice guideline recommendations for previously untreated patients were modified after considering new data. The modified recommendations did not deviate substantially from the original recommendations and, therefore, were not circulated for external review.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

Previously Untreated Patients with Intermediate- or High-Risk Chronic Lymphocytic Leukemia

- As first line treatment in patients with intermediate- or high-risk chronic lymphocytic leukemia, fludarabine or conventional chemotherapy (chlorambucil) are acceptable treatment options. Fludarabine improves progression-free survival but has a greater risk of toxicity, including specific infections.
- Patient preferences and clinical judgement should influence choice of treatment. Factors to be considered in selecting treatment should include the route of drug administration and balancing the benefits of potential longer progression-free survival with increased risks of treatment-related toxicity.

Previously Treated Patients with Intermediate- or High-Risk Chronic Lymphocytic Leukemia

The evidence in previously treated patients with intermediate- or high-risk chronic lymphocytic leukemia is based on one randomized controlled trial of fludarabine versus cyclophosphamide, Adriamycin, prednisone, and six phase II studies. The randomized controlled trial detected superior response and a trend towards improved progression-free survival with fludarabine, but overall survival was not significantly different.

- Fludarabine is an acceptable treatment option after failure of first-line therapy.
- Choice of treatment should be influenced by previously used regimens and patient preference.

Dosing and Special Considerations

- Based on recommendations put forward by the Canadian Blood Services and the British Committee for Standards in Hematology Blood Transfusion Task Force, it is recommended that patients who have been treated with fludarabine receive irradiated blood products because of the risk of transfusion related graft versus host disease.
- Autoimmune hemolytic anemia may be exacerbated or precipitated by fludarabine and is, therefore, considered by the manufacturer to be a contraindication to the use of this drug.
- A dose of 25 mg/m^2 per day for five consecutive days intravenously every four weeks for a total of six cycles, or two cycles beyond maximum response is suggested.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

September 1998 Guideline

Four studies examined fludarabine in previously untreated patients, three randomized controlled trials (RCTs) and one phase II study. Seven studies examined fludarabine in previously treated patients, one randomized controlled trial and six phase II studies.

February 2002 Update

Since the development of the original guideline, eight published articles and seven abstract reports were found during the updating process. Of the published articles, four update or provide other additional information to randomized trials previously reported only in abstract form, and included in the initial guideline report. One of these updates describes the infectious complications seen in a trial comparing chlorambucil, fludarabine, and a combination of both agents; another reports quality of life outcomes evaluated in the trial completed by the French Cooperative Group. Two publications were systematic reviews, including an individual patient data meta-analysis. The seventh full publication describes a randomized phase II trial comparing high-dose chlorambucil with fludarabine in previously untreated patients and the eighth publication is a trial of oral fludarabine. In addition, two systematic reviews, including one meta-analysis, have since been reported. The CLL Trialists Collaborative Group has pooled the results of randomized trials to evaluate the role of timing and choice of chemotherapy in previously untreated patients. The Swedish Council of Technology Assessment in Health Care (SBU) reported results of a systematic literature review assessing the role of observation, and standard- and high-dose therapy, including autologous and allogeneic transplantation, in patients with B-cell chronic lymphocytic leukemia. Previously untreated and treated patients were included. Forty-four publications involving 11,289 patients were reviewed and included 11 publications (five full articles describing three trials, and six abstracts) that evaluated the role of fludarabine.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

September 1998 Guideline

- In previously untreated patients with intermediate- or high-risk chronic lymphocytic leukemia, the pooled analysis for response rates between fludarabine and conventional treatments from the 3 randomized controlled trials yielded an overall odds ratio of 2.44, favoring fludarabine over conventional treatments (95% confidence interval (CI), 1.65 to 3.61; $p<0.00001$). Long-term survival data are lacking.
- For previously treated patients, preliminary results report longer progression-free survival with fludarabine compared with chlorambucil or cyclophosphamide-Adriamycin-prednisone (CAP). In previously treated

patients with intermediate- or high-risk chronic lymphocytic leukemia, the one available randomized controlled trial detected a superior response rate for fludarabine (48%; 95% CI, 33 to 63; n=48) compared with cyclophosphamide-Adriamycin-prednisone (27%; 95% CI, 15 to 42; n=48) but no survival advantage (median survival [months] for fludarabine was 23.9 and for cyclophosphamide-Adriamycin-prednisone was 24.0; p-value, not significant). Long-term survival data from this randomized controlled trial are lacking.

February 2002 Update

- A randomized trial comparing fludarabine, and the combination of fludarabine plus chlorambucil, with chlorambucil alone in patients with previously untreated intermediate- or high-risk chronic lymphocytic leukemia, was previously reported in abstract form and has now been updated in a full report. In comparison with chlorambucil, fludarabine treatment is associated with a superior complete remission rate and progression-free survival. However, no difference in overall survival was detected.
- A randomized trial compared fludarabine with two anthracycline-containing regimens (cyclophosphamide, doxorubicin, vincristine and prednisone; and cyclophosphamide, doxorubicin, and prednisone) in previously untreated patients with chronic lymphocytic leukemia. In comparison with cyclophosphamide-doxorubicin-prednisone, treatment with both fludarabine and cyclophosphamide, doxorubicin, vincristine and prednisone resulted in superior overall and complete response rates. No differences in overall survival or incidence of infections were detected.

POTENTIAL HARMS

September 1998 Guideline

Fludarabine is associated with significant myelosuppression and immunosuppression, and an increased risk of opportunistic infection. Cases of transfusion-related graft versus host disease have been described and therefore it is recommended that patients receiving this drug receive irradiated blood products. Autoimmune hemolytic anemia, a condition associated with chronic lymphocytic leukemia (CLL), may be exacerbated or precipitated by fludarabine and is thus considered by the manufacturer to be a contraindication to the use of this drug. Uncommonly reported adverse effects include neurologic and pulmonary toxicity and tumor lysis syndrome. For details on the adverse effects, refer to the body of the (original guideline) report.

February 2002 Update

A randomized trial comparing fludarabine, and the combination of fludarabine plus chlorambucil, with chlorambucil alone in patients with previously untreated intermediate- or high-risk chronic lymphocytic leukemia found that the risk of infection, particularly with herpes viruses, is greater in patients receiving fludarabine. Combining fludarabine and chlorambucil resulted in more severe myelosuppression and more frequent infections. Combination therapy was also associated with a greater incidence of myelodysplasia and acute myeloid leukemia (3.5%) as compared with fludarabine alone (0.5%) or chlorambucil alone (0%).

CONTRAINDICATIONS

CONTRAINDICATIONS

Autoimmune hemolytic anemia may be exacerbated or precipitated by fludarabine and is, therefore, considered by the manufacturer to be a contraindication to the use of this drug.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

September 1998 Guideline

None stated

February 2002 Update

- An updated report of a randomized control trial in previously untreated patients with chronic lymphocytic leukemia demonstrated that patients treated with fludarabine plus chlorambucil had higher rates of infection and therapy-related myelodysplasia or acute myeloid leukemia than did patients treated with chlorambucil alone. This combination should be avoided outside the setting of research studies.
- The same trial also demonstrated that patients treated with fludarabine had higher rates of infection, especially with herpes viruses, than did patients treated with chlorambucil.
- The guideline developers had previously suggested that patients treated with fludarabine receive prophylactic treatment with cotrimoxazole to prevent infections with pneumocystis carinii. The incidence of pneumocystis in a randomized study evaluating previously untreated patients that did not include routine prophylaxis was very low (3 of 518 patients), suggesting that routine prophylaxis for these patients is unwarranted.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Cancer Care Ontario Practice Guideline Initiative (CCOPGI). Fludarabine in intermediate-and high-risk chronic lymphocytic leukemia [full report]. Toronto (ON): Cancer Care Ontario (CCO); 2002 Feb. Various p. (Practice guideline; no. 6-1). [45 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1999 Apr 6 (updated online 2002 Feb)

GUIDELINE DEVELOPER(S)

Practice Guidelines Initiative - State/Local Government Agency [Non-U.S.]

GUIDELINE DEVELOPER COMMENT

The Practice Guidelines Initiative (PGI) is the main project of the Program in Evidence-based Care (PEBC), a Province of Ontario initiative sponsored by Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

SOURCE(S) OF FUNDING

Cancer Care Ontario, Ontario Ministry of Health and Long-Term Care

GUIDELINE COMMITTEE

Provincial Hematology Disease Site Group; Systemic Treatment Disease Site Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

For a current list of the Hematology Disease Site Group members, please see the Cancer Care Ontario Web site.

For a current list of the Systemic Treatment Disease Site Group members, please see the Cancer Care Ontario Web site.

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Members of the Hematology Disease Site Group and the Systemic Treatment Disease Site Group disclosed potential conflict of interest information.

GUIDELINE STATUS

This is the current release of the guideline.

The FULL REPORT, initially the full original Guideline or Evidence Summary, over time will expand to contain new information emerging from their reviewing and updating activities.

Please visit the Cancer Care Ontario Web site for details on any new evidence that has emerged and implications to the guidelines.

GUIDELINE AVAILABILITY

Electronic copies: Available from the Cancer Care Ontario Web site.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Fludarabine in intermediate- and high-risk chronic lymphocytic leukemia. Summary. Toronto (ON): Cancer Care Ontario, 1999 Apr 6 (updated online 2002 Feb). Electronic copies: Available from the Cancer Care Ontario Web site.
- Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. J Clin Oncol 1995;13(2):502-12.

PATIENT RESOURCES

None available

NGC STATUS

This summary was completed by ECRI on August 19, 1999. The information was verified by the guideline developer as of September 17, 1999. This NGC summary was updated by ECRI on December 3, 2001. The updated information was reviewed by the guideline developer as of January 10, 2002. This summary was updated on July 30, 2003. The updated information was verified by the guideline developer on September 2, 2003.

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